

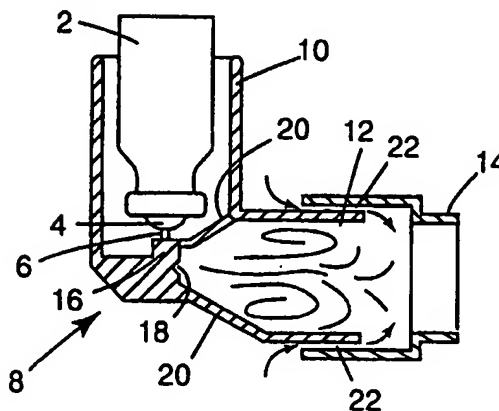
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(54) Title: SLOW SPRAY METERED DOSE INHALER**(57) Abstract**

A pressurised metered dose inhaler having an actuator constructed and arranged so as to inhibit airflow due to patient inhalation in the vicinity of the orifice of the nozzle block when the valve stem is in its dispensing position. This design reduces unwanted oropharyngeal deposition of medicament and increases the relative amount of medicament to the lung.



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SLOW SPRAY METERED DOSE INHALER

FIELD OF THE INVENTION

This invention relates to an inhaler for medicament and in particular to an inhaler
5 for transferring to the respiratory system of a patient a metered dose of medicament
contained in a pressurised dispensing canister.

BACKGROUND OF THE INVENTION

In known metered dose inhalers, the aerosol stream comprising liquefied propellant
10 and medicament from a pressurised dispensing canister is fired into a chamber towards a
mouthpiece of the inhaler into an air space that allows airflow travelling in the same
direction via openings to the outside air. In known devices at actuation, a user inhales
through a mouthpiece of the inhaler and creates an airflow through the chamber from air
inlets which are generally at a part of the inhaler located upstream from the mouthpiece.
15 Upon actuation, the medicament is then released into this airflow at a point between the air
inlets and the mouthpiece so that it is travelling in the same direction as the airflow.
Typically in such devices, there is little restriction in the airflow between the air inlets and
the mouthpiece. Because of this, a substantial airflow may be created by a user of the
device and, because the medicament is fired into the airflow in the same direction as the
20 airflow, the effect is that particles of medicament can be travelling at quite substantial
velocities e.g. in excess of 40m/s when they reach the mouthpiece. As inhalers of this type
are normally designed to be as small as practical for the convenience of users, the distance
between the point at which the medicament is fired into the airflow and the patient's mouth
is usually quite small so that there is little distance to reduce the inertia of the particles of
25 medicament with the result that the particles may impact and deposit in the oropharynx
rather than being carried with inhaled air into the lungs. This is normally quite
undesirable, since the medicaments were designed for delivery to the respiratory system
and may not have an appropriate effect when deposited in the oropharynx and allowed to
enter the digestive tract.

30 In an effort to overcome this problem, devices have been produced in which the
medicament is fired into a holding volume, commonly called a Spacer, which allows the
velocity of the medicament to be reduced and also allows some propellant evaporation to
occur. Spacers can improve the performance of a metered dose inhaler by reducing

oropharyngeal deposition, see S.P. Newman & S.W. Clarke, Chest, vol 103 (5) pp. 1442-1446 (1993) Bronchodilator Delivery From Gentlehaler, A New Low-Velocity Pressurized Aerosol Inhaler and S.P. Newman, A.R. Clark, N. Talee & S.W. Clarke, Thorax, vol 44 pp.706-710 (1989), Pressurised aerosol deposition in the human lung with and without an "open" spacer device.

However, these devices with a holding volume and other spacer devices tend to be of significantly larger size than the conventional metered dose inhalers and therefore less convenient and attractive to users.

Various attempts have been made to modify the spray characteristics of inhalers.

GB-A-2279879 discloses an inhaler in which the air inlets are arranged such that during inhalation an airflow is created which has a component directed away from the mouthpiece towards the aerosol spray. The reverse airflow component is intended to create turbulence and slow the velocity of the medicament particles.

WO93/05837 and US-A-4972830 disclose inhalers in which the passage which directs the pressurised medicament from the canister to the chamber has particular configurations to reduce the velocity of the spray and enhance dispersion of the medicament in the airflow.

EP-A-0412648 discloses an inhaler in which a frusto-conical diverter with a small orifice is positioned in the path of the spray before the mouthpiece. Aerosol droplets are said to predominantly pass through the small orifice, decelerate and be inhaled while the propellant gas is predominantly diverted away from the mouthpiece out of the inhaler.

It is known to modify the airflow through an inhaler to achieve particular effects. WO93/09830 discloses an inhaler which is constructed and arranged to prevent inhalation through the device prior to the dose being fired. The object of the arrangement is to synchronise inhalation and firing the dose to ensure the dose is dispensed during inhalation. US-A-5758638 discloses an inhaler which includes an air port so that during inhalation flow of air through the port activates an audio or visual signal generates, such as a whistle or flag, that signals to the user that the user is inhaling and that the conditions are appropriate for the administration of the medicament.

Similarly for intranasal inhalers it is desirable to reduce the velocity of the spray in the interests of patient comfort and efficacy.

SUMMARY OF THE INVENTION

The present invention provides alternative constructions of an inhaler which reduce the velocity of the spray exiting the mouthpiece or nasal adapter.

According to the present invention there is provided an inhaler for medicament
5 comprising an aerosol canister containing a pressurised medicament formulation equipped with a metered dose dispensing valve having a valve stem movable between non-dispensing and dispensing positions, and an actuator comprising a housing adapted to receive the aerosol container and defining a chamber having one or more air inlets and a patient port in the form of a mouthpiece or nasal adapter, and a nozzle block adapted to
10 receive the valve stem of the dispensing valve, the nozzle block comprising a passage in communication with the valve stem and terminating in an orifice for directing medicament from the valve stem into the chamber, in which the actuator is constructed and arranged to inhibit patient-induced airflow in the vicinity of the orifice of the nozzle block when the valve stem is in its dispensing position.

15 The inhaler of the invention may be constructed such that airflow due to patient inhalation is prevented or reduced in the vicinity of the orifice at all times or only during dispensing of the medicament from the valve. Either arrangement has the effect of substantially reducing the velocity of the emitted spray compared to an inhaler which allows free flow of air in the vicinity of the nozzle block during dispensing of the
20 medicament. It is possible to modify existing press and breathe inhalers to prevent such airflow by the provision of a suitable gasket.

It has been discovered that the velocity of an aerosol spray from a metered dose inhaler is significantly influenced by the presence of an open conduit in the vicinity of the nozzle through which the spray emerges. The spray exits the nozzle as a high velocity
25 stream which creates low pressure regions. The ability of the free-flowing air entering through air vents to fill the low pressure regions influences the velocity of the emitted spray. If a free flow of air is allowed in the vicinity of the nozzle, as in a standard press-and-breathe inhaler where the patient breathes through the mouthpiece and an airflow is established around the canister and nozzle to the mouthpiece, the emitted spray maintains
30 a high velocity. If the actuator is sealed to outside airflow in the vicinity of the nozzle, the low pressure regions cannot immediately be occupied by the surrounding air and the low pressure regions exert a retarding influence on the stream emanating from the nozzle, thereby causing the stream to lose velocity.

It has been found that inhibiting make-up, or free-flowing air in the vicinity of the nozzle when the spray is generated significantly reduces the velocity of the emitted spray and spray force from the mouthpiece, resulting in an extremely soft, low velocity spray plume.

5 The vicinity of the orifice includes on all sides upstream to the temporary or permanent closure behind the nozzle block, and downstream to the first communication with the outside atmosphere. That is, during dispensing there is no communication to the outside atmosphere for the region surrounding the orifice of the nozzle block. There is no communication with the outside atmosphere via the air inlets upstream to the orifice of the
10 nozzle block and no communication with the outside atmosphere downstream of the orifice of the nozzle block for a distance sufficient to allow the aerosol stream to develop sufficient turbulence to stop its downstream momentum. For example, the stream exiting 0.30mm to 0.50mm orifice would not be in communication with the outside atmosphere via the upstream air inlets and the stream would be in communication with outside air
15 being drawn into the device at a downstream distance relative to the orifice of 4 to 6cm. The location downstream of the orifice at which the outside air is drawn into the device may vary from 0 to 15cm depending on the orifice diameter and mouthpiece diameter.

 Radioscintigraph tests have revealed that when airflow is prevented or restricted in the vicinity of the nozzle the flow of the spray becomes turbulent within the chamber. The
20 turbulent zone is generally formed between about 3 to 5cm from the nozzle for a nozzle orifice of approximately 0.30mm. The high degree of turbulence causes a large reduction in the linear velocity of the spray as well as an increase in the deposition of drug particles on the wall of the chamber. If the chamber and mouthpiece are of sufficient length to encompass this turbulent zone the result is a significant reduction in the kinetic energy of
25 the stream delivered to the patient. Preferably, the actuator is constructed such that the distance from the nozzle to the mouthpiece is from approximately 1 to 15cm, preferably 4 to 6cm, with a chamber/mouthpiece diameter from 1 to 4 cm, 0.5 to 1cm in the case of a nasal adapter.

The actuator must possess air inlets which enable the patient to inhale through the patient port without encountering significant resistance since the patient may have breathing difficulties when taking the medication e.g. during an asthma attack. However, the air inlets, for example in the mouthpiece, must not concentrate the airflow into too narrow an area, as this will give a high velocity of incoming air which will deflect the spray onto the wall of the mouthpiece opposite the air inlets.

In one embodiment of the invention the air inlets are positioned downstream of the nozzle, in the region of the turbulent zone and/or downstream of the turbulent zone. The positioning and direction of the air inlets may also affect the deposition of medicament within the chamber and mouthpiece. In one arrangement air inlets comprise a series of holes, within or downstream of the turbulent zone adjacent the mouthpiece directing air perpendicular to the aerosol stream. In a second arrangement the air inlets are directed towards the outlet of the mouthpiece to introduce a sheath of air around the aerosol stream, parallel to the aerosol stream. In a third arrangement the air inlets are arranged, optionally interspersed with baffles on the wall of the chamber, to direct air into the turbulent zone to mix air with the aerosol stream. In a fourth arrangement the air inlets are positioned at the downstream end or downstream of the turbulent zone and direct air back towards the turbulent zone. In a further arrangement a mouthpiece is constructed of porous material to allow a multiplicity of finely divided air vents to provide air flow over a larger surface area. The diffuse airflow through the mouthpiece also tends to keep the formulation stream away from the mouthpiece wall, thereby reducing drug deposition on the walls.

In a second embodiment of the invention the actuator may possess air inlets upstream of or in the vicinity of the nozzle but the air inlets are blocked when the valve is fired to release the aerosol spray. The air inlets are opened after the spray has been released by which time the velocity of the stream will have been reduced and the turbulent zone formed. Upon inhalation an airflow will be established from the air inlets to the mouthpiece which entrains the residual aerosol spray. The actuator may include additional air inlets downstream of the nozzle, as described above with respect to the first embodiment. These downstream air inlets do not need to close during release of the aerosol spray.

A third embodiment uses a porous membrane to introduce air into or downstream of the turbulent zone. The advantage of the membrane is that the air is introduced more uniformly and diffusely around the circumference of the spray, thereby acting as a buffer

between the turbulent flow and the wall. The effect is to reduce drug deposition in the device. The membrane may optionally be protected from dirt or contact by the users lips by an additional part of the mouthpiece. This embodiment may be used in combination with embodiment 1 or 2. Additionally, this embodiment may be incorporated without the
5 restricting or preventing of airflow in the vicinity of the nozzle.

For certain medicaments it is particularly desirable to reduce contact between the medicament and parts of the body it is not intended for. For example, residues of the medicament deposited on internal surfaces of actuators may be fingered and transferred to other body parts. A fourth embodiment of the invention incorporates a baffle to allow the
10 spray to pass through, whilst limiting access by the patient to internal surfaces of the actuator.

A fifth embodiment of the invention is configured for intranasal delivery.

It is known that the size of the orifice in the nozzle may affect the spray characteristics. Smaller orifices tend to produce aerosols of small droplet size which lead
15 to improved respirable fraction. However, smaller orifices are more difficult to manufacture. The actuator of the invention significantly reduces the spray velocity regardless of the orifice size. It has been shown to reduce oropharyngeal deposition with orifices in the size range 0.010 to 0.025 inch and the deposition for these two sizes was found not to differ significantly.

20

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described with reference to the accompanying drawings in which:

Figure 1 represents a cross-section through an inhaler in accordance with one
25 embodiment of the invention,

Figure 2 represents a cross-section through an inhaler according to a second embodiment of the invention,

Figure 3 represents a diagrammatic cross-section of a portion of an inhaler in accordance with a further embodiment of the invention,

30 Figure 4 represents a partial diagrammatic cross-section of a further inhaler in accordance with the invention,

Figures 5a, 5b and 5c represent a cross-section of a further inhaler in accordance with the invention,

Figures 6 to 9 represent cross-sectional views of further inhalers in accordance with the invention.

Figures 10(a) and (b) represent cross-sectional views of a further inhaler in accordance with the invention in its firing and rest positions respectively,

5 Figure 11 represents a cross-sectional view of a further inhaler in accordance with the invention in its firing position, Figures 11(a) to 11(c) illustrating alternative baffles for the mouthpiece thereof and

Figures 12a and b represent a perspective view and cross-sectional view of a nasal inhaler in accordance with the invention.

DETAILED DESCRIPTION

10 The inhaler of Figure 1 comprises an aerosol canister (2) equipped with a metered dose dispensing valve (4) having a valve stem (6). The actuator, generally shown at (8), comprises a housing (10) which receives the aerosol container (2), a chamber (12) and a
15 mouthpiece (14). A nozzle block (16) receives the valve stem (6) and has a passage (not shown) terminating in an orifice (18) which directs spray from the aerosol valve into the chamber. The housing comprises solid walls (20) in the vicinity of the nozzle block so that there can be no air flow through the device in the vicinity of the orifice. Air inlet
20 passages (22) are positioned towards the end of the chamber (12) and are directed towards the mouthpiece (14).

When the aerosol valve is fired, a metered dose of aerosol formulation exits the orifice (18) in to chamber (14). There is no air flow in the vicinity of the orifice (18). Consequently the spray is rapidly decelerated and a turbulent zone is formed shown
25 generally by the curved lines within the chamber (12). As the patient breathes through the mouthpiece (14) air passes through the inlets (22) towards the mouthpiece (14) forming a sheath of air around the spray of aerosol formulation. The inhaler provides substantially reduced deposition in the oropharynx of the patient compared with a standard press-and-breathe inhaler without compromising the respirable fraction unduly.

30 Figure 2 of the accompanying drawings illustrates a second embodiment of the invention which is similar to Figure 1 and like numerals represent like parts. The difference in the embodiment shown in Figure 2 is that the mouthpiece (14) has a bulbed configuration (24) to provide an increase in cross-sectional area of the mouthpiece downstream of the turbulent zone followed by a decrease in cross-sectional area at the

extreme downstream end of the mouthpiece. The arrangement of air inlets is similar to that shown in Figure 1, the bulbed configuration acts in a similar manner to a conventional spacer.

Figure 3 is a diagrammatic cross-section through a portion of an inhaler having an alternative construction of air inlets. In this embodiment the air inlets (30) are arranged downstream of the nozzle block and have associated baffles (32) such that incoming air is deflected in to the turbulent zone of the aerosol spray shown by the curved lines within the chamber (12). The air inlets and baffles can extend throughout the circumference of the chamber or may be located towards the bottom of the chamber. The baffles may continue throughout the length of the chamber to the mouthpiece to facilitate turbulence of the airflow.

Figure 4 of the accompanying drawings is a diagrammatic cross-section of a portion of an inhaler in accordance with the invention. The downstream end of the chamber is shaped to form a venturi (34) and the air inlet ports (36) are arranged such that air enters in a direction towards the turbulent zone. The aerosol spray is expanded through the venturi as it reaches the mouthpiece (14).

Figures 5a to 5c represent a cross-section through an alternative inhaler in accordance with the invention. In this embodiment, when the valve (4) is in its non-dispensing position air inlet ports (40) formed between the canister (2) and the housing (10) are open (Figure 5a). When the valve (4) is in its dispensing position caused by moving the canister (2) relative to the valve stem (6) (Figure 5b), seal 42 around the canister (2) closes the air inlet ports (40). Thus, during firing of the aerosol spray, there is no airflow in the vicinity of the orifice (18) and the spray will decelerate and form a turbulent zone within the chamber (12) shown by the curved lines. Thereafter, the patient releases the canister (2) which returns the valve to the non-dispensing position (Figure 5c) and during inhalation at the mouthpiece (14) an airflow is established through the air inlets (40) to the mouthpiece (14) via the chamber (12) thereby entraining the medicament in the inspired air.

The inhaler of Figure 6 is based upon the inhaler of Figure 5 and incorporates additional air inlets (22) of the type disclosed in Figure 1.

The inhaler of Figure 7 is based upon the inhaler of Figure 5 and incorporates a mouthpiece (14) having a bulbed configuration (24) and air inlets (22) of the type disclosed in Figure 2.

The inhaler of Figure 8 is based upon the inhaler of Figure 5 and incorporates air inlets in the form of a microporous membrane (50) which is positioned downstream of the turbulent zone adjacent the mouthpiece (14). The arrangement provides a multiplicity of finely divided air inlets which, upon inhalation through the mouthpiece, creates a diffuse
5 airflow which keeps the emitted stream away from the wall of the mouthpiece.

The porous membrane material (50) must not significantly impede the patient's ability to inhale through the device. A suitable material is Whatmann No. 4 filter paper; but other materials may be used, such as those used in cylindrical air filters or membrane filters, or such as those formed by sintering polymers. A preferred porous membrane
10 material is in the form of a cylinder made by fusing together small pellets of polypropylene.

The inhaler of Figure 9 is similar to that of Figure 8 and additionally comprises a shield (52) to protect the microporous membrane (50) from contamination. The shield is constructed to provide air inlets (22) to direct air towards the microporous membrane (50).

15 The inhaler of Figure 10 is similar to that of Figures 5, except that the air inlet ports (54) are closed between the flat surface of the valve ferrule (56) and a parallel ledge (58) within the actuator, by means of a seal (60), when the inhaler is in its dispensing position.

Figure 11 shows an embodiment like that in Figure 10, with a baffle (62) inserted.
20 The baffle can form part of a mouthpiece component (14), like those in Figures 6 to 9. Alternatively, it can form part of a mouthpiece (64) which provides a sheath of air that emerges at the extreme downstream end of the inhaler. The skilled person will also appreciate that the mouthpiece (64) can substitute for mouthpiece (14) in Figures 6 to 9. The baffle is in the form of a thin disc defining a plurality of circular passages (65)
25 therethrough. Preferably, there are a large number of circular passages and their accumulated area makes up a substantial proportion of the disc area as illustrated in Figure 11a. The mouthpiece (64) has a plurality of passages (66) parallel to its axis and disposed through its circumference.

Figures 11b depicts a component with an alternative baffle which consists of a thin
30 disc with a single circular hole (68).

Figure 11c depicts another component in which the baffle consists of a disc with two kidney-shaped holes (69).

Figures 12a and 12b illustrate an inhaler for nasal administration of medicament.

The inhaler (80) comprises a body (82) and a nosepiece (84) which is dimensioned so that it may be inserted in a nostril without being an airtight fit. The body (82) has an aperture (86) to receive the valve stem (not shown) of the pressurised aerosol, an orifice (88) communicating with a chamber (90) leading to the nosepiece (84). The valve stem forms a gas-tight seal within the orifice (88).

In use the nosepiece is inserted in a nostril and the patient inhales while actuating the valve of the pressurised aerosol container. Inhalation does not cause airflow through the inhaler (80) but an airflow is established around the outside of the nosepiece and medicament exiting the nosepiece is entrained in the airflow and delivered to the respiratory system of the patient.

The inhalers of the invention which are intended for pulmonary delivery reduce the oropharyngeal deposition. Preferred inhalers of the present invention are capable of providing improvements both in terms of oropharyngeal and lung deposition. For example, the inhaler of Figure 8 produced a greater lung deposition and smaller oropharyngeal deposition than a metered dose inhaler fitted with a standard actuator available under the trade designation M3756 from 3M. The inhalers were compared by sealing against a cast of an upper airway and firing into air drawn through at 30 litres per minute (D.J. Velasquez and B. Gabrio 1998 J. Aerosol Med. 11 (Suppl. 1) : S23-S28). The aerosol which passed through the airway was collected on a HEPA filter. Both inhalers contained beclomethasone dipropionate formulated as a radiolabelled solution. In the Table below the amount assayed by radioscintigraphy in the cast is designated 'oropharyngeal' and the amount in the filter is designated 'lung'. The inhaler produced a drug particle size equivalent to that produced by the standard inhaler with a mass median diameter of 1.4 micrometers.

| | Standard MDI | Slow spray device |
|-----------------|--------------|-------------------|
| % oropharyngeal | 35.3 | 10.0 |
| % lung | 44.2 | 54.2 |

Another advantage of inhalers of the invention is that the consequences of poor co-ordination of inhalation with actuation of the inhaler are improved compared with a

- standard inhaler. Disco-ordination tests were conducted on a standard press and breathe metered dose inhaler and a similar inhaler which had been modified in accordance with the invention to operate in principle as that disclosed in Figure 1. The inhalers were tested using the equipment described above. A delay of 1 second between actuation and start of
- 5 inhalation resulted in the following change in percentage regional deposition.

Change in percentage regional deposition

| | Percent Change in Deposition | | |
|--------------|------------------------------|------------|------|
| | Device | Oropharynx | Lung |
| Invention | +15 | -3 | -12 |
| Standard MDI | +41 | +8 | -49 |

CLAIMS

1. An inhaler for medicament comprising an aerosol canister containing a pressurised medicament formulation equipped with a metered dose dispensing valve having a valve stem movable between non-dispensing and dispensing positions, and an actuator
5 comprising a housing adapted to receive the aerosol container and defining a chamber having one or more air inlets and a patient port in the form of a mouthpiece or nasal adapter, and a nozzle block adapted to receive the valve stem of the dispensing valve, the nozzle block comprising a passage in communication with the valve stem and terminating in an orifice for directing medicament from the valve stem into the chamber, characterised
10 in that the actuator is constructed and arranged so as to inhibit airflow due to patient inhalation in the vicinity of the orifice of the nozzle block when the valve stem is in its dispensing position.
2. An inhaler as claimed in Claim 1 characterised in that it is constructed and arranged such that airflow due to patient inhalation is prevented or inhibited in the vicinity
15 of the orifice at all times.
3. An inhaler as claimed in Claim 1 characterised in that airflow due to patient inhalation is not prevented or inhibited in the vicinity of the orifice at all times.
4. An inhaler as claimed in any preceding Claim in which the distance from the orifice to patient port is from 1 to 15cm, and preferably 4 to 6cm and the mouthpiece
20 diameter between 1 to 4cm.
5. An inhaler as claimed in any preceding Claim in which air inlet ports are positioned near the end of the chamber adjacent the mouthpiece and/or in the mouthpiece.
6. An inhaler as claimed in Claim 5 in which the air inlets are directed towards the exit of the mouthpiece.
- 25 7. An inhaler as claimed in Claim 5 in which the air inlets are directed perpendicular to the direction of the orifice.
8. An inhaler as claimed in Claim 5 in which the air inlets are directed towards the nozzle block.
9. An inhaler as claimed in Claim 6 in which the wall of the chamber and/or
30 mouthpiece comprises baffles to deflect the air inwardly.
10. An inhaler as claimed in Claim 5 in which the air inlets comprise a multiplicity of numerous, small air channels which serve to provide a large surface area for air to enter

the mouthpiece.

11. An inhaler as claimed in Claim 10 in which the air inlets are in the form of a microporous membrane.
12. An inhaler as claimed in Claim 11 in which the microporous membrane is
5 protected from contamination and/or contact with the patient's lips by a shield.
13. An inhaler as claimed in Claim 3 in which the air inlets are formed between the canister and housing when the valve is in its non-dispensing position and the air inlets are sealed when the valve is in its dispensing position.

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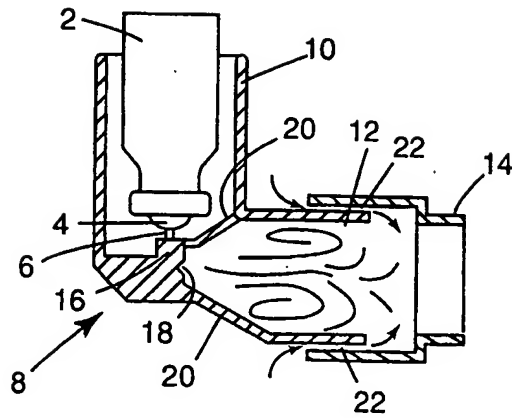


Fig. 1

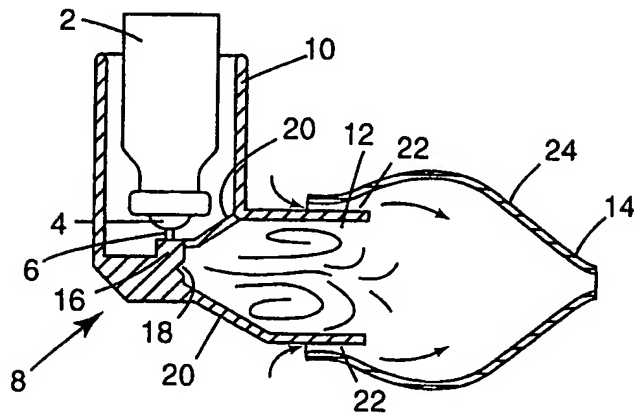


Fig. 2

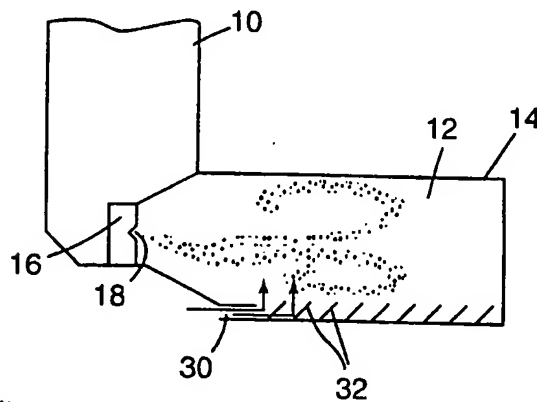
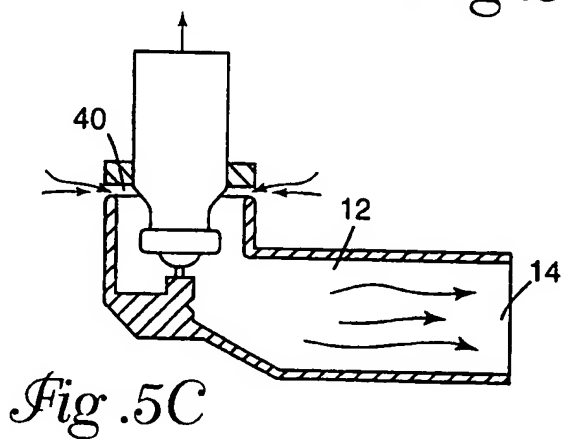
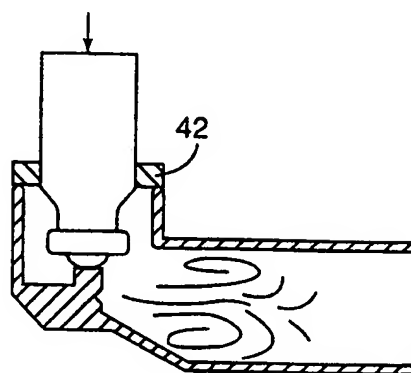
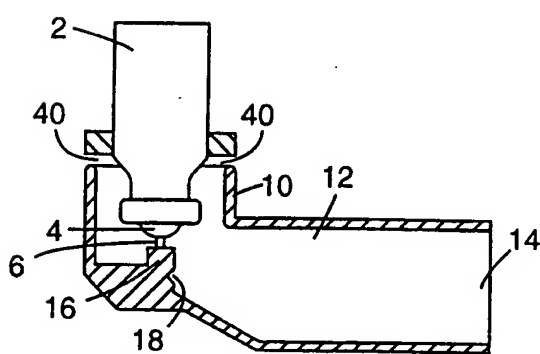
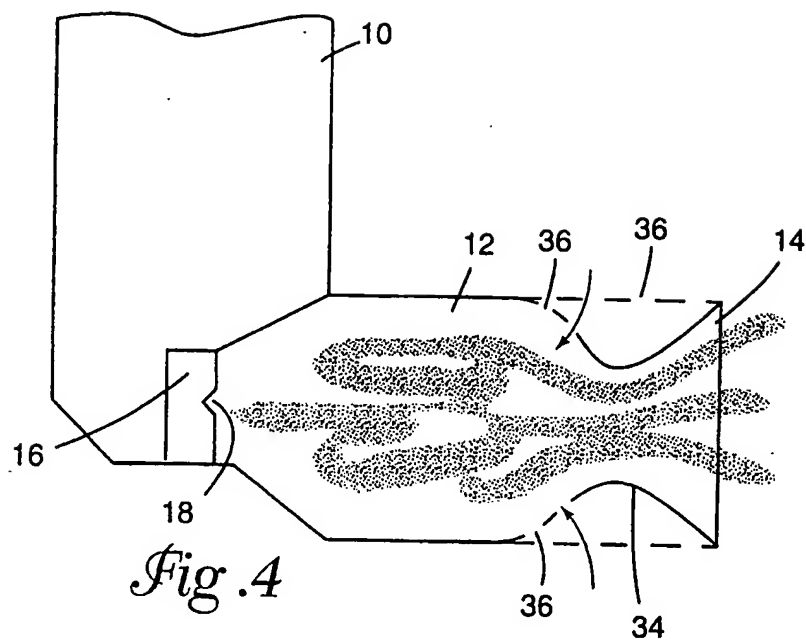
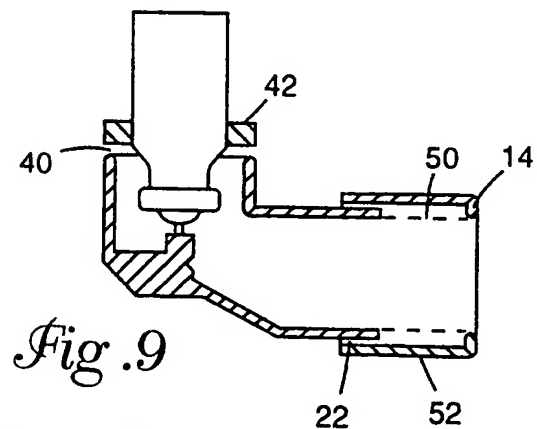
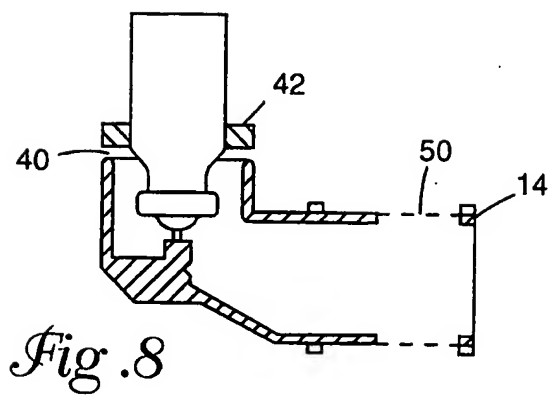
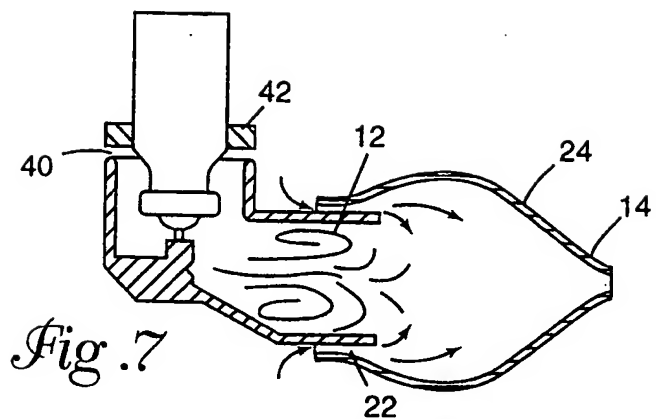
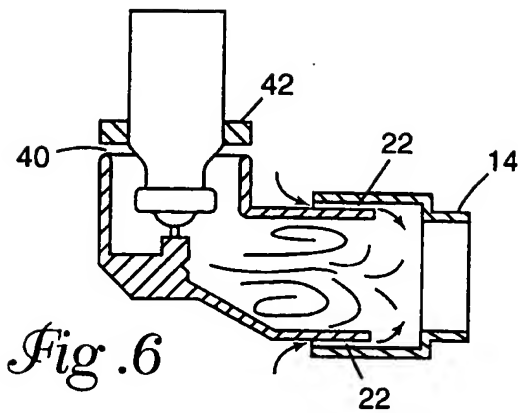


Fig. 3





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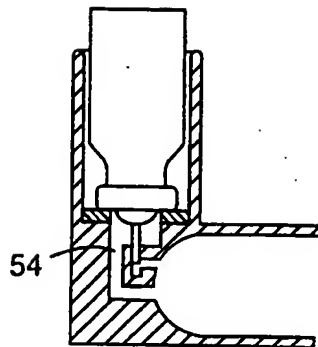


Fig. 10a

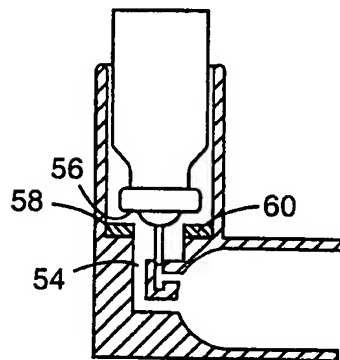


Fig. 10b

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Fig. 11

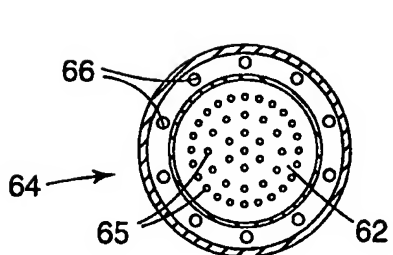
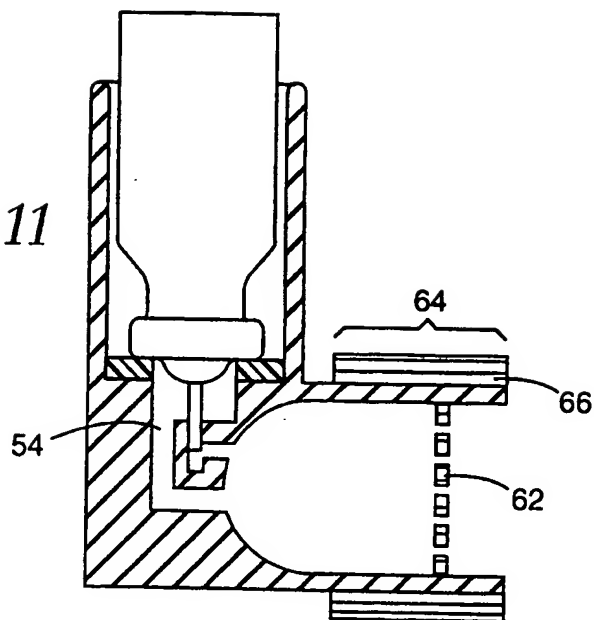


Fig. 11a

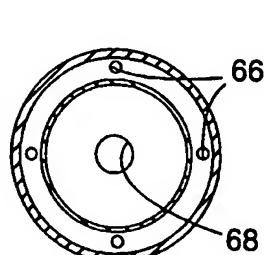


Fig. 11b

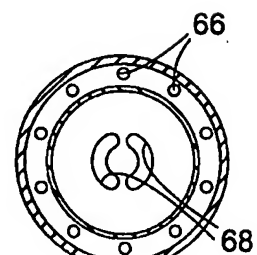


Fig. 11c

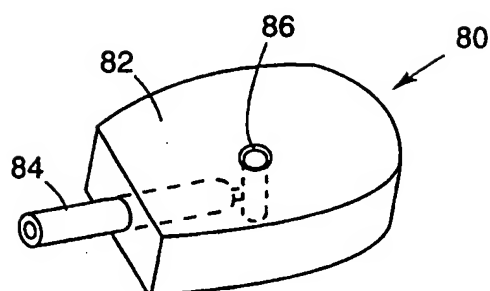


Fig. 12a

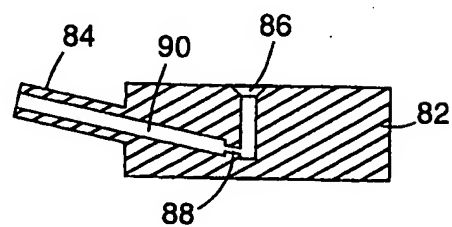


Fig. 12b

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/04984

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| Y | claim 1; figures | 5,8 |
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| | page 6, last paragraph; claim 1 | |
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

29 June 2000

Date of mailing of the international search report

10/07/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2

NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,

Fax: (+31-70) 340-3016

Authorized officer

Villeneuve, J-M

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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